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Privileged Communication

PTEN, energy metabolism and tumor suppression

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The tumor suppressor 'phosphatase and tensin homolog deleted on chromosome 10' (PTEN) is frequently mutated or deleted in many types of tumors. PTEN germline mutations have been found in several familial cancer predisposition syndromes such as Cowden syndrome, Lhermitte–Duclos disease, Bannayan–Riley–Ruvalcaba syndrome and Proteus and Proteus-like syndromes. As a lipid phosphatase, PTEN dephosphorylates phosphatidylinositol 3,4,5-trisphosphate (PIP3), the second messenger produced by phosphatidylinositol 3-kinase (PI3K), and therefore negatively regulates the PI3K/AKT signaling pathway. The PI3K/AKT pathway plays a critical role in driving cell proliferation and cell survival, which is frequently activated in tumors and contributes to tumorigenesis. Loss of PTEN leads to the accumulation of PIP3, which in turn recruits phosphatidylinositol-dependent kinase 1 (PDK1) and AKT to plasma membrane where PDK1 phosphorylates and activates AKT. By negative regulation of the oncogenic PI3K/AKT pathway, PTEN functions as a tumor suppressor [1]. Interestingly, a recent study by Garcia-Cao *et al.* [2] reported a new role of PTEN in the negative regulation of cellular energy metabolism; PTEN elevation in mice (Super-PTEN mice) shifts cellular metabolism to a tumor-suppressive metabolic state by negative regulation of two key metabolic pathways, glycolysis and glutaminolysis, through both PI3K/AKT-dependent and PI3K/AKT-independent pathways. This study strongly suggests that the function of PTEN in metabolic regulation could contribute significantly to the role of PTEN in tumor suppression.

Metabolic alterations have been regarded as a hallmark of tumor cells. Unlike majority of normal cells that depends on mitochondrial oxidative phosphorylation to provide energy, most tumor cells primarily utilize aerobic glycolysis for their energy needs, a switch known as the Warburg effect [3]. Glycolysis is a much less efficient ATP-generating pathway, which produces two ATPs per glucose molecule, compared with mitochondrial oxidative phosphorylation, which produces 36 ATPs per glucose molecule. Therefore, tumor cells compensate by having a much higher rate of glucose uptake and utilization than normal cells. On the basis of the Warburg effect, positron emission tomography has been established and widely used for tumor detection as tumors take up more ^{18}flurodeoxyglucose, a radioactive glucose analog, than normal tissues. The Warburg effect has recently been shown to have an important role in the maintenance of malignancies by conferring tumor cells advantages of proliferation and survival [4–6]. Although the Warburg effect has attracted much of our attention on cancer metabolism for the past decades, cancer cells also need excess amino acids, lipids, and nucleotides for rapid growth and proliferation through a number of metabolic alterations occurring in cancer cells in addition to the Warburg effect. For instance, many tumors show altered metabolism of glutamine [7]. Glutamine, a non-essential amino acid for human beings, can be used for synthesis of proteins and nucleotides, and providing energy for the rapidly growing and proliferating tumor cells. Glutamine can be converted into glutamate by glutaminase, which can be further converted into α-ketoglutarate, an important substrate for the tricarboxyclic acid cycle to produce ATP in cells (glutaminolysis). Enhanced glutaminolysis has been observed in many tumors [7].

The molecular mechanisms underlying the Warburg effect are not well understood although the Warburg effect was discovered almost 90 years ago. Recent studies have started to uncover the underlying mechanisms. The activation of several oncogenes has been shown to contribute to the Warburg effect, including Akt, Myc, and hypoxia inducible factor-1α (HIF-1α) in cancer cells [4–6]. AKT, the main downstream target negatively regulated by PTEN, is a critical regulator of the glycolytic pathway. AKT has been shown to enhance glycolysis by inducing the translocation of glucose transporters, glucose transporter (GLUT) 1 and GLUT4, to the plasma membrane [8]. Glucose transporters mediate the transport of glucose across the plasma membrane of cells, which is the first rate-limiting step for glucose metabolism. Furthermore, AKT

activates glycolytic enzymes, such as hexokinase 2 and phosphofructokinase 1 and 2 [4–6]. AKT also stimulates glycolysis through direct phosphorylation and inactivation of tumor suppressor tuberous sclerosis protein 2, a negative regulator of mammalian target of rapamycin complex-1 (mTORC1), which functions as a key metabolic integration point and promotes glycolysis in cells. Myc transcriptionally activates many of the glycolytic enzymes, including lactate dehydrogenase A (LDHA), hexokinase 2, phosphofructokinase, and enolase 1 as well as GLUT1 [4–6]. In addition to the activation of glycolysis, Myc promotes glutaminolysis through directly up-regulating the expression of the glutamine transporters SLC38A5 and SLC1A5, which increase glutamine uptake into cells. Furthermore, Myc can repress the expression of miR-23a and miR-23b, two microRNAs that down-regulate the expression of glutaminase (GLS) 1, the first rate-limiting enzyme of glutaminolysis [9]. As a common feature of solid tumors, hypoxia has been regarded as a driving force to switch cellular metabolism from mitochondrial oxidative phosphorylation to glycolysis, thereby promoting the Warburg effect in cancer cells [4–6]. HIF-1α is stabilized under the hypoxic conditions and stimulates glycolysis through direct transactivation of glucose transporter GLUT1, as well as many glycolytic enzyme genes, such as LDHA and pyruvate kinase M2 (PKM2). Furthermore, HIF-1α induces pyruvate dehydrogenase kinase 1, which in turn phosphorylates and inactivates pyruvate dehydrogenase, an enzyme that catalyzes the conversion of pyruvate into acetyl-CoA and serves as a critical link between glycolysis and mitochondrial oxidative phosphorylation, thereby repressing the mitochondrial oxidative phosphorylation and stimulating glycolysis. In addition to hypoxia, HIF-1α can also be stabilized by activation of AKT and Ras, or high rates of aerobic glycolysis itself, resulting in increased glycolysis in cancer cells [10,11].

In addition to the activation of oncogenes, recent studies show that tumor suppressor p53 plays a critical role in preventing the Warburg effect in cells [5,12]. As a transcription factor, p53 mainly exerts its function through the transcriptional regulation of its target genes. p53 enhances the mitochondrial oxidative phosphorylation by inducing the expression of synthesis of cytochrome c oxidase 2 and GLS2, and reduces the glycolysis by inducing the expression of 'TP53-induced glycolysis and apoptosis regulator (TIGAR)' and Parkin [13–16]. In addition, p53 regulates glucose metabolism through inhibiting the NF-κB pathway to reduce the levels of glucose transporter GLUT3 and down-regulate glycolysis [17], or interacting with glucose-6-phosphate dehydrogenase to inhibit the pentose phosphate pathway [18]. Loss of p53 leads to the Warburg effect in both cultured tumor cells and in mouse models. Considering that p53 is mutated in over 50% of human tumors, loss of p53 function should be an important genetic change accounting for the Warburg effect in tumors. In addition to the inhibition of the Warburg effect, recent studies further show that p53 regulates lipid metabolism through transcriptional regulation of guanidinoacetate methyltransferase and Lpin1 (lipin 1) [19,20]. Results from these studies strongly suggest that maintaining the homeostasis of cellular metabolism is an important function of p53, which contributes to p53′s role as a tumor suppressor.

In this recent report, Garcia-Cao *et al*. [2] show that in addition to p53, PTEN is another tumor suppressor which plays a critical role in regulation of metabolism in cells. They generated transgenic Super-PTEN mice, which carry additional copies of PTEN gene and express elevated levels of PTEN. Interestingly, the PTEN elevation in these mice results in a healthy and tumor-suppressive metabolic state through the modulation of both PI3K/AKT-dependent and PI3K/AKT-independent pathways. The Super-PTEN mice are cancer resistant, and cells from the mice are resistant to oncogenic transformation. Super-PTEN mice exhibit increased energy expenditure, reduced body fat accumulation, and reduced body weight and size. Furthermore, unlike the function of AKT in drosophila in controlling both cell number and cell size, PTEN elevation results in a reduced body size due to reduced cell number but not cell size. Super-PTEN cells have reduced glucose and glutamine uptake and increased mitochondrial oxidative phosphorylation. In addition to the reduced activities of the PI3K/AKT pathway, a well-characterized downstream of PTEN which stimulates glycolysis in tumor cells, PTEN elevation results in decreased levels of two rate-limiting enzymes of glycolysis: PKM2 and 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3). Both PKM2 and PFKFB3 are overexpressed in many tumors. PTEN elevation reduces PKM2 levels through negative regulation of mTORC1, which induces PKM2 expression, and promotes PFKFB3 degradation through the E3 ubiquitin ligase APC/Cdh1 complex. Furthermore, PTEN elevation leads to the reduced levels of GLS1, the first rate-limiting enzyme in glutaminolysis, also through the enhanced degradation of GLS1 by the APC/Cdh1 complex. Therefore, Super-PTEN cells exhibit reduced glutaminolysis in addition to the reduced glycolysis. The results from this study demonstrated that PTEN negatively regulates glycolysis and glutaminolysis, two most pronounced metabolic features of tumor cells, which could contribute significantly to the role of PTEN in tumor suppression. These results also revealed that the loss of PTEN is an important mechanism for the increased glycolysis and glutaminolysis in tumor.

The role of metabolism in tumorigenesis and tumor therapy is an area of growing interest. Recent studies have strongly suggested that as a hallmark of cancer cells

metabolic alterations in cancer could be targeted for the development of new cancer therapies. Considering the critical role of PTEN in repressing glycolysis and glutaminolysis in cancer cells, it will be of interest to study whether those tumors with loss of PTEN function are more sensitive to combined inhibition of glycolysis and glutaminolysis, which could be a potential therapeutic approach for those tumors. Increasing evidence has demonstrated that many oncogenes (such as AKT, Myc, HIF-1α) and tumor suppressor genes (such as p53 and PTEN) regulate cellular metabolism, and alterations of these genes in cancer cells greatly impact upon many aspects of cancer metabolism including the Warburg effect. These findings strongly suggest that metabolic alterations are an important underlying mechanism for tumorigenesis. Future studies would further shed light on how oncogenes and tumor suppressor genes regulate cellular metabolism, and how the alterations of these genes in cancer impacts on different aspects of cancer metabolism in addition to the Warburg effect. Such studies will lead to our further understanding of the molecular mechanisms of cancer, and help to find the potential Achilles' heel of cancer cells, which will contribute to the development of metabolic therapy for cancer treatment.

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